

PRION DEMENTIA

Information for Wisconsin Medical Providers from the Wisconsin Division of Public Health and the Prion Disease Advisory Workgroup*

Introduction

The Wisconsin Division of Public Health (DPH) is in the process of making human Transmissible Spongiform Encephalopathy (TSE) an officially reportable condition. Clinicians are strongly encouraged to report suspected TSE cases to the DPH. TSEs consist of any prion-related disease, including sporadic Creutzfeldt-Jakob Disease (sCJD), new variant Creutzfeldt-Jakob Disease (vCJD), Fatal Familial Insomnia and Gerstmann-Sträussler-Scheinker Syndrome. Of these, only sCJD is known to occur with any frequency in the US (incidence ~ 1 per million).

A workgroup consisting primarily of Wisconsin neurologists and neuropathologists was convened to develop the clinical criteria that should elicit a report of a possible TSE case. This expert panel has also developed guidelines to assist health care providers in the management /diagnosis of suspected prion-related dementias and has established a referral network consisting of clinicians with expertise in prion diseases. This document discusses these clinical guidelines and the referral network.

Criteria for Reporting a Suspect Case of TSE in Wisconsin

A prion-related disorder, such as Creutzfeldt-Jakob Disease (CJD), should be suspected and reported to the Wisconsin Division of Public Health in any patient with:

Dementia of early onset (<55 years) *OR*

Rapidly progressive dementia with one or more of the following:

- Movement disorders (e.g., myoclonus, ataxia)
- Painful sensory symptoms
- Visual disturbances

To report a case, call Jim Kazmierczak, DVM, at the Division of Public Health at 608-266-2154

Diagnosis and Work-Up

It is the choice of the clinician whether to manage a patient with a suspected prion disease or whether to refer the patient to a specialty center or neurologist as discussed below. As in any patient with dementia, treatable causes should first be sought. Routine blood work would include a CBC, electrolytes, hepatic and renal function tests, B12 level and thyroid testing.

A careful neurological history and examination may reveal findings supportive of a diagnosis of a TSE, such as an insidious, nonspecific prodrome (fatigue, behavioral change, depression, weight loss, sleep disturbance), leading within months to relentless dementia, with prominent neurological signs such as myoclonus, ataxia, visual disturbance, corticospinal and extrapyramidal dysfunction, and akinetic mutism.

Confirmatory diagnostic studies include:

- **Cerebrospinal fluid**: constituents are usually normal, except for elevated levels of the 14-3-3 neuron-specific enolase; sensitivity and specificity may approach 90%, however the usefulness of this test is questionable early in the disease. Research is ongoing to determine when in the course of the illness this becomes positive.
- **Electroencephalogram**: early in sCJD the EEG may be normal or may show non-specific slowing; later biphasic or triphasic synchronous complexes may be superimposed on a slow background; terminally, the EEG will show periodic sharp wave complexes in up to 90% of patients. These characteristic EEG findings are usually absent in cases of vCJD.
- **Magnetic Resonance Imaging**: CJD typically shows increased T2 and FLAIR signal in the basal ganglia and cerebral cortex in ~ 80% of patients at presentation. Diffusion-weighted MRI sequences are critical for optimal detection, with sensitivity and specificity approaching 100% in the appropriate clinical setting. *For this reason, it is essential to order a diffusion-weighted-MRI study and consult with an experienced neuroradiologist when considering the diagnosis of CJD.*
- **Brain biopsy and Autopsy**: Conventional pathological investigation will show spongiform encephalopathy and will allow submission of tissues to the national registry laboratory for specialized studies. We **strongly** recommend specimens be sent to the National Prion Disease Pathology Surveillance Center, Institute of Pathology, Case Western Reserve University, Cleveland, OH. Telephone: 216-368-0587, e-mail cjdsurv@po.cwru.edu. This Center can also perform genotyping on frozen specimens to determine the type of CJD and diagnose related conditions such as GSS and FFI. These services are offered free of charge.
- **Infection Control Considerations – Autopsy and Embalming**: World Health Organization (WHO) Infection Control Guidelines for Transmissible Spongiform Encephalopathies (TSE) should be followed during autopsy. An autopsied or

traumatized body of a suspected or confirmed TSE patient can be embalmed using the precautions outlined in the WHO TSE Infection Control Guidelines. www.who.int/emc-documents/tse/docs/whocdscsraph2003.pdf. Bodies that have not been autopsied or traumatized can be embalmed using Standard Precautions.

- **Funding for Autopsies:** Funds are available through the Division of Public Health to provide for transport for autopsy and / or autopsy costs of suspect TSE patients at a Wisconsin prion disease center. Please contact Dr. Jim Kazmierczak at 608-266-2154 for details.

Differential Diagnosis of CJD and other Prion Dementias

The differential diagnosis of CJD includes treatable conditions such as B12 deficiency, hypothyroidism, syphilis, other central nervous system infections (HIV/AIDS, chronic meningitis, Whipple's disease etc), cerebrovascular disease, direct and indirect (paraneoplastic) effects of cancer, Wilson's disease, normal pressure hydrocephalus, toxic exposure, organ failure, psychiatric disorders, unusual presentation of Parkinson's disease or Parkinson-plus syndromes, and others.

Incurable conditions which may enter into the differential diagnosis of CJD include unusual presentations of Alzheimer's disease, Pick's disease, diffuse Lewy body disease, frontotemporal dementia, corticobasilar degeneration, mitochondrial diseases, leukodystrophies, and spinocerebellar degenerations.

New variant CJD (vCJD) was linked to beef consumption during the occurrence of a large outbreak of bovine spongiform encephalopathy (BSE, commonly known as mad cow disease) among cattle in the United Kingdom (UK) in the 1990's. To date, despite an active USDA surveillance program, no case of this cattle disease has been identified in the US. The vCJD should not be confused with the classic form of sCJD that is endemic throughout the world. The median age at death of patients with sCJD is 68 years and very few cases occur in persons under 30 years of age. In contrast, the median age at death of patients with vCJD in the UK is 28 years. The vCJD can be confirmed only through examination of brain tissue. The incubation period for vCJD is unknown; however, it is likely that it will be measured in years or decades. In contrast to sCJD, vCJD in the UK predominantly affects younger people, has atypical clinical features, with prominent psychiatric or sensory symptoms at the time of clinical presentation and delayed onset of neurologic abnormalities, including ataxia within weeks or months, dementia and myoclonus late in the illness, a duration of illness of at least 6 months and a diffusely abnormal non-diagnostic EEG.

Further Resources: Wisconsin Prion Centers and Neurologists

A network of medical centers and neurologists in Wisconsin has been established in order to assist health care professionals in the diagnosis, care, and reporting of possible human prion disease such as CJD. At each center, there are identified neurologists, neuro-radiologists, neuropathologists, and other professionals with expertise in prion diseases available for consultation or referral. If you would like to refer a patient to one of the centers, please call **Jim Kazmierczak, at the Wisconsin Division of Public Health, 608-266-2154**. Dr. Kazmierczak will fax this document and other pertinent information to the caller.

The goals of the network are to assist primary clinicians and neurologists in the accurate diagnosis of patients with suspected prion diseases, advise on the care of persons with prion diseases, promote public safety, enhance reporting to state health officials for surveillance purposes, and facilitate interactions with national prion research centers.

Tier 1

Prion Centers	City	Contact Person	Phone	E-mail
University of Wisconsin	Madison	John O. Fleming, MD	608-263-5421	fleming@neurology.wisc.edu
Marshfield Clinic	Marshfield	Susan F. Mickel, MD	715-387-5351	mickel.susan@marshfieldclinic.org
Medical College of Wisconsin	Milwaukee	Malgorzata Franczak, MD	414-805-5224	mfran@mcw.edu

Tier 2

Referral Neurologists	City	Phone	E-mail
John O. Fleming, MD	Madison	608-263-5421	fleming@neurology.wisc.edu
Benjamin R. Brooks, MD	Madison	608-263-5421	brooks@neurology.wisc.edu
Susan F. Mickel, MD	Marshfield	715-387-5351	mickel.susan@marshfieldclinic.org
Malgorzata B. Franczak, MD	Milwaukee	414-805-5224	mfran@mcw.edu
Gizelle R. Larson, MD	Neenah	920-725-9373	gizell.larson@thedacare.org
Piero G. Antuono, MD	Milwaukee	414-805-5224	antuono@mcw.edu
Vincent T. Miller, MD	Chippewa Falls	715-726-4123	miller.vincent@marshfieldclinic.org

*Wisconsin Prion Disease Advisory Workgroup: Benjamin R. Brooks, MD; John O. Fleming, MD; Malgorzata B. Franczak, MD; Bradley C. Hiner, MD; Khang-Cheng Ho, MD, PhD; Jeffrey M. Jentzen, MD; Susan F. Mickel, MD; Vincent T. Miller, MD; Denis C. Nathan, MD; Robert J. Przybelski, MD, MS; Roger E. Riepe, MD; Howard A. Rowley, MD; M. Shahriar Salamat, MD, PhD.